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Pantoprazole Affecting Docetaxel Resistance Pathways via Autophagy (PANDORA): Phase II Trial of High Dose Pantoprazole (Autophagy Inhibitor) with Docetaxel in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Key Words. Metastatic castration-resistant prostate cancer • Autophagy inhibition

Abstract

Background. Enhancing the effectiveness of docetaxel for men with metastatic castration-resistant prostate cancer (mCRPC) is an unmet clinical need. Preclinical studies demonstrated that high-dose pantoprazole can prevent or delay resistance to docetaxel via the inhibition of autophagy in several solid tumor xenografts.

Materials and Methods. Men with chemotherapy-naive mCRPC with a prostate-specific antigen (PSA) >10 ng/mL were eligible for enrolment. Men received intravenous pantoprazole (240 mg) prior to docetaxel (75 mg/m^2) every 21 days, with continuous prednisone 5 mg twice daily. Primary endpoint was a confirmed ≥50% decline of PSA. The trial used a Simon's two-stage design.

Results. Between November 2012 and March 2015, 21 men with a median age of 70 years (range, 58–81) were treated (median, 6 cycles; range, 2–11). Men had received prior systemic therapies (median, 1; range, 0–3), and 14 had received abiraterone and/or enzalutamide. PSA response rate was 52% (11/21), which did not meet the prespecified criterion (≥13/21 responders) to proceed to stage 2 of the study. At interim analysis with a median follow-up of 17 months, 18 (86%) men were deceased (15 castration-resistant prostate cancer, 2 unknown, 1 radiation complication). Of the men with RECIST measurable disease, the radiographic partial response rate was 31% (4/13). The estimated median overall survival was 15.7 months (95% confidence interval [CI], 9.3–19.6) and median PFS was 5.3 months (95% CI, 2.6–12.9). There were no toxic deaths, and all adverse events were attributed to docetaxel.

Conclusion. The combination of docetaxel and pantoprazole was tolerable, but the resultant clinical activity was not sufficient to meet the ambitious predefined target to warrant further testing. ***The Oncologist*** 2019;24:1188–1194

Implications for Practice: To date, no docetaxel combination regimen has reported superior efficacy over docetaxel alone in men with metastatic castration-resistant prostate cancer (mCRPC). The PANDORA trial has demonstrated that the combination of high dose pantoprazole with docetaxel is tolerable, but the clinical activity was not sufficient to warrant further testing. The chemotherapy standard of care for men with mCRPC remains docetaxel with prednisone. Future studies of autophagy inhibitors will need to measure autophagy inhibition accurately and determine the degree of autophagy inhibition required to produce a meaningful clinical response.

Introduction

Autophagy is a highly conserved adaptive process that maintains homeostasis by metabolizing cytoplasmic waste in the setting of cellular stressors such as inflammation, hypoxia, and nutrient depletion. Cells in solid tumors can use autophagy to meet increased nutrient demand, thereby enabling tumor progression. The degree of autophagy has been associated

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with poor prognostic outcomes in various solid tumors [1–4]. In the setting of cellular distress induced by chemotherapy, autophagy can promote cancer cell survival and resistance to treatment. Several clinical and preclinical models demonstrated that high levels of autophagy were correlated with resistance to systemic therapy, including androgen deprivation treatment in prostate cancer [5–13].

High doses of the H+/ATPase proton pump inhibitor pantoprazole can prevent the acidification of endosomes and their fusion with autophagosomes to inhibit autophagy [12]. Pantoprazole was shown to augment tumoricidal effects of chemotherapy by enhancing drug distribution relative to tumor blood vessels, modifying acidity of the tumor microenvironment and inhibiting autophagy [12–14]. Our preclinical studies have demonstrated that high doses of pantoprazole modulated autophagy in several solid tumor xenografts and prevented or delayed resistance to the microtubule inhibitor docetaxel [14]. In a 24-patient, phase I study of pantoprazole combined with doxorubicin, we observed no unexpected toxicities and declared the recommended phase II dose of pantoprazole to be 240 mg intravenously every 3 weeks [15].

Herein we report the results of a single arm, single center phase II trial (PANDORA) of high-dose pantoprazole with docetaxel (and prednisone) in patients with metastatic castration-resistant prostate cancer (mCRPC). The objective of this study was to determine the efficacy and safety of this combination. Our hypothesis was that the addition of pantoprazole would increase the frequency of prostate-specific antigen (PSA) response and delay the time to PSA progression in men with mCRPC treated with docetaxel and prednisone without additional adverse events.

Methods and Materials

Trial Design

PANDORA (NCT01748500) was conducted at the Princess Margaret Cancer Centre. This was a prospective, single arm, Simon two-stage, phase II trial. An independent data and safety monitoring committee was commissioned to review safety data on a regular basis. The trial received local research ethics board approval. All men provided written informed consent prior to participation, and the trial was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines.

Patients and Treatment

Eligible men were required to be at least 18 years old and have Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, normal organ function, and pathologically confirmed prostate cancer. All men must have had a PSA ≥10 ng/mL, clinical or radiographic evidence of metastatic disease, with progression while receiving androgen deprivation therapy defined as an increase in PSA of ≥25% (and an absolute increase of ≥2 ng/mL) over the nadir value on three successive occasions at least 1 week apart, with a testosterone level <50 ng/dL (<1.7 nmol/L). Antiandrogen therapy must have been stopped at least 4 weeks prior to start of trial treatment (6 weeks for bicalutamide or nilutamide) if there was a reduction in serum PSA after this therapy was initiated. If there was no response then no washout was necessary. No washout was required for enzalutamide or abiraterone acetate. Men who had received prior chemotherapy or radioisotopes for prostate cancer were excluded.

Pantoprazole was given prior to docetaxel, at a dose of 240 mg intravenously over 30 minutes. Docetaxel was started 30 minutes after the end of pantoprazole infusion and was administered in a 21-day dosing cycle at 75 mg/m^b body-surface area. Prednisone 5 mg b.i.d. was taken continuously by all participants in addition to their androgen deprivation therapy.

End Points

The primary endpoint of this study was confirmed PSA response (early rises within 12 weeks were ignored) protocol defined as a decrease in PSA of ≥50% from baseline, which was maintained for ≥3 weeks. Secondary end points were time to PSA progression, progression-free survival (PFS), overall survival (OS), and toxicity.

Assessments

Efficacy assessments included sequential radiographic imaging to assess radiographic progression-free survival (computed tomography [CT] or magnetic resonance imaging [MRI] and bone scanning) performed every 12 weeks. PSA levels were measured at baseline and with each cycle of treatment until the end of trial treatment. Participants underwent serial monitoring of vital signs, serum hematologic and chemical findings, liver-function tests, and serum testosterone levels. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0.

Biomarkers

Archived, paraffin-embedded prostate tumor samples were obtained to evaluate markers of autophagy by using immunohistochemistry (IHC) to stain for p62 and microtubule-associated protein 1 light chain 3B (LC3B) [16, 17]. p62 protein is a surrogate marker of autophagic degradation; it recognizes toxic cellular waste and is constantly degraded in autolysosomes. Lack of autophagy leads to accumulation of p62, and nuclear localized p62 has been reported to increase sensitivity of tumor cells to radiation [18]. Conversely, absent p62 staining is associated with high autophagy and greater resistance to docetaxel [12, 14]. LC3B identifies autophagosome formation, and high LC3B staining is associated with high levels of autophagy. p62 and LC3B have been demonstrated to be in constant flux between nuclear and cytoplasmic compartments [19, 20]; thus, we performed both nuclear and cytoplasmic staining of p62 and LC3B. Blood samples were also collected for pharmacokinetic analysis and to evaluate carbonic anhydrase IX (Ca IX), as a surrogate measure of tumor hypoxia, because autophagy is upregulated in the presence of hypoxia [13]. Human Ca IX Quantikine ELISA kit was used to measure Ca IX levels in serum (R&D systems Inc, Minneapolis, MN).

Pain and Quality of Life

All study participants were required to complete the present pain intensity scale of the McGill-Melzack questionnaire [21]

and to keep a diary of their daily intake of analgesic medication at baseline and prior to each chemotherapy cycle. The pain score varies between 0 and 5 with verbal descriptors; higher numbers indicate greater pain. Analgesic intake was used to compute an analgesic score (AS), representing the average daily intake of pain medication during the past week, using 4 points for a standard dose of oral narcotics (e.g., morphine 10 mg, hydromorphone 2 mg) and 1 point for a standard dose of non-narcotics. Participants evaluable for the secondary endpoint of pain response had pain score ≥2 and/or AS ≥10 at baseline. Pain response required a fall in pain score by ≥2 points and/or a decrease in AS by ≥50%, without increase in either, maintained for at least 3 weeks. Duration of pain response was recorded.

Participants completed the FACT-P questionnaire [22, 23]. Responses were summed to give an overall quality of life (QoL) score ranging from 0–156, where higher numbers indicate better QoL. Participants evaluable for the secondary endpoint of QoL response must have a QoL score of ≤126 at baseline (≤80% of perfect score). QoL response required an improvement of QoL score of ≥16 points (or ≥10%), maintained for at least 3 weeks, as used in the TAX 327 study [24].

Pharmacokinetic Analysis

A planned analysis of 10–12 patients was performed to evaluate pharmacokinetic interactions between pantoprazole and docetaxel. Three 6 mL blood samples were drawn at the following time points during the first cycle of treatment: (a) just before start of docetaxel infusion, (b) immediately after the 1 hour docetaxel infusion, and (c) 2 hours after docetaxel infusion.

Statistical Analysis

This trial used a Simon's two-stage design. Based on an improvement in PSA response rate of 25% from an expected value of 50% for docetaxel/prednisone alone (H_0 = 0.5 and H_A = 0.75) with α = 0.05 and β = 0.1, 32 patients were planned for enrollment. The first stage would recruit 21 evaluable patients and if 13 or more patients responded the trial would progress to stage II. PFS and OS were assessed by the Kaplan-Meier method. Kappa coefficient was used to calculate concordance between different IHC stains, and Fisher's exact test was used to determine associations between IHC stains with PSA and RECISTv1.1 responses. Wilcoxon's test was used to determine associations between Ca IX baseline levels and change in Ca IX quantities with PSA and RECIST responses. No correction was made for the multiple statistical tests. SAS 9.2 (SAS Institute Inc., Cary, NC) was used for the analysis.

Results

Patients and Treatment

A total of 21 men were enrolled from January 2013 to March 2015. The baseline demographics and treatment history are outlined in Table 1. Of those enrolled, 13 (62%) had RECIST measurable disease. The median number of prior lines of treatment in the mCRPC setting was 1 (range 0–3). Fourteen (67%) of the 21 men had received prior abiraterone and/or enzalutamide. The median number of docetaxel cycles administered was 6, with a range from 2–11.

Table 1. Participant demographics

Characteristic	Frequency (*n* = 21)
Age, median (range), yr	70 (58–81)
ECOG performance status 0:1:2	9:11:1
Prior therapy, *n* (%)	
Abiraterone	11 (52)
Enzalutamide	6 (29)
Both abiraterone and enzalutamide	3 (14)
Investigational drug	4 (19)
Prior radiation, *n* (%)	
Prostate	9 (47)
Metastases or recurrence	9 (47)
Prior prostatectomy, *n* (%)	5 (24)
Time from diagnosis to castration resistance, median (range), mo	39 (10–170)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

End Points

The number of PSA responders was 11 (52%). Of the men with RECIST measurable disease, the radiographic partial response rate was 31% (4/13). No man (0%) who had received both abiraterone and enzalutamide responded to the study treatment. Three men who had prior abiraterone only responded (3/8, 37.5%), and three men who had prior enzalutamide only responded (3/3, 100%). Five (71%) responses were seen in the seven men who had neither abiraterone or enzalutamide. At time of analysis, 18 (86%) men were deceased (15 from disease, 2 unknown cause, and 1 radiation complication). The median OS was 15.7 (95% confidence interval [CI], 9.3–19.6) months and the median PFS was 5.3 (95% CI, 2.6–12.9) months (Fig. 1A, 1B, respectively).

Safety

The adverse events (AEs) observed on trial were reviewed by an independent data safety monitoring board (DSMB). No major findings were identified by the DSMB. Table 2 outlines the AEs reported on study. The addition of pantoprazole did not appear to increase the frequency of AEs as compared with docetaxel monotherapy. There were no toxic deaths and all adverse events were attributed to docetaxel. The dose of 240 mg intravenous (IV) pantoprazole every 3 weeks with 75 mg/m^b of docetaxel every 3 weeks was a safe and tolerable dose. The most frequent all grade AEs included fatigue (81%), nausea (62%), and anorexia (38%). The most common grade 3 or 4 AEs were fatigue (24%), anemia (19%), febrile neutropenia (14%), grade 4 neutropenia (14%), and anorexia (5%).

Biomarkers

Nineteen men had samples from either their diagnostic prostate biopsies (14) or their definitive radical prostatectomies (5) analyzed for p62 and LC3B expression (Table 3). Of these, 18 (95%) samples had cytoplasmic expression of p62 but only 6 (32%) had concordant cytoplasmic and nuclear p62 staining. In contrast, cytoplasmic and nuclear

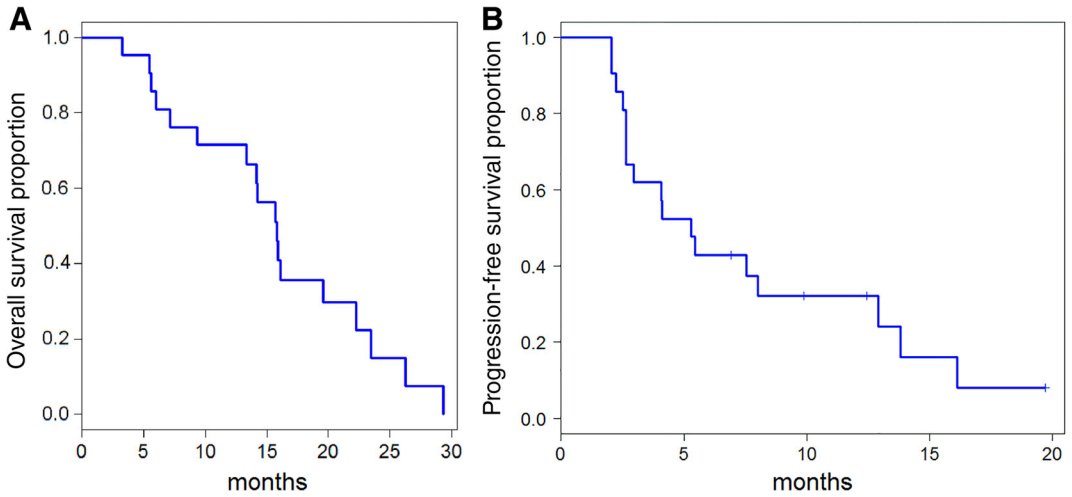

Figure 1. Kaplan-Meier curves. **(A):** Overall survival. **(B):** Progression-free survival. The median OS was 15.7 (95% confidence interval [CI], 9.3–19.6) months and the median PFS was 5.3 (95% CI, 2.6–12.9) months.

Table 2. All grade and grade ≥3 adverse events

Adverse event	All grade (*n* = 21)	Grade ≥3 (*n* = 21)	Worst grade of AE
Fatigue	17	5	3
Nausea	13	0	2
Alopecia	12	0	2
Anorexia	8	1	3
Dysguesia	7	0	2
Peripheral edema	6	0	2
Mucositis	6	0	2
Peripheral sensory neuropathy	6	0	2
Anemia	5	4	4
Diarrhea	5	0	2
Febrile neutropenia	3	3	3
Neutropenia	3	3	4

Abbreviation: AE, adverse event.

LC3B expression was concordant in 14 (74%) tumors (κ = 0.51, 95% CI, 0.09–0.92). Cytoplasmic and nuclear LC3B staining was not associated with nuclear p62 expression (κ = –0.07; CI, –0.40 to 0.25 and κ = –0.07; CI, –0.40 to 0.25, respectively). Nuclear p62 expression was associated with a radiographic (RECIST) response to study treatment (Table 4), with three (75%) responders having nuclear p62 expression. The expression of nuclear p62 was not associated with OS or PSA response.

All but one participant (95%) had pretreatment baseline Ca IX level analyzed. The median Ca IX pretreatment level in blood was 56 pg/mL (range, 15–291). Nineteen patients had post-cycle 4 Ca IX levels drawn (patient 1004 and 1008 had Q1055 assessment at 2 and 3 cycles, respectively). The median Ca IX post-treatment quantity was 45 pg/mL (range, 15–489). There were 18 pre- and post-treatment pairs available for comparison. Six pairs had an increase in Ca IX quantities (33%) from pre- to post-treatment, and 11 (61%) pairs had a decrease in Ca IX levels. One pair showed no change in Ca IX levels. Neither baseline Ca IX levels nor change in Ca IX levels from pre- to post-treatment measure were correlated with PSA response (p = .52 and p = .21 respectively) or RECIST response (p = .38 and p = .20, respectively). There was no association between baseline Ca IX levels and nuclear p62 staining (p = .83). There was no association between Ca IX levels at baseline or cycle 4 with OS (p = .74 and p = .44, respectively).

Table 3. Results of autophagy markers

IHC stain	p62 nuc	p62 cyto	LC3B nuc	LC3B cyto
No expression	14	1	6	6
Any expression	5	18	13	13
Missing samples	2	2	2	2
Concordant nuc and cyto result	6	6	14	14

Abbreviations: Cyto, cytoplasmic; IHC, immunohistochemistry; nuc, nuclear.

Pain and QoL Responses

Fifteen (71%) men were evaluable for pain response. In total, nine (43%) men had a pain response that was maintained for a minimum of 3 weeks, with a median duration of response of 63 days (range, 21–148). Five (24%) patients had a QoL response by the FACT-P score that was maintained for a minimum of 3 weeks, with a median duration of response of 64 days (range, 21–85).

Pharmacokinetic Analysis

A total of 13 men had paired samples for pharmacokinetic analysis. At 1 hour, docetaxel concentration ranged from 147 to 12,100 ng/mL (mean, 2,966 ± 3,709), and at 3 hours, docetaxel concentration ranged from 21 to 1,440 ng/mL (mean, 211.6 ± 376).

Discussion

In this single arm, nonrandomized phase II study, high-dose pantoprazole was added to standard of care docetaxel with prednisone for men with mCRPC. The study did not meet its ambitious predefined endpoint of 13 or more PSA responses in

Table 4. Association between p62 nuclear staining and PSA response and RECIST response

	PSA response			RECIST response		
p62 nuclear	**No**	**Yes**	**Total**	**No**	**Yes**	**Total**
No expression	9 (64)	5 (36)	14	7 (100)	0 (0)	7
Any expression	1 (20)	4 (80)	5	1 (25)	3 (75)	4
Total	10	9	19	8	3	11
p value[a]	.141	.141	.141	.024	.024	.024

[a]Fisher's exact test (two-sided).
Abbreviation: PSA, prostate-specific antigen.

the first 21 participants. In the men with RECIST measurable disease, the overall response rate was higher than that seen historically in men treated with docetaxel and prednisone alone, albeit in a small number of patients [24].

One potential explanation for the lack of PSA responders to the experimental regimen is prior treatment with either abiraterone and/or enzalutamide. The PSA response rate in patients who received prior abiraterone and/or enzalutamide was 43% (6/14), which was considerably lower compared with those men who had not received either of those agents. Attenuated PSA response rates or resistance to docetaxel following treatment with these hormonal agents has been demonstrated and this may have diluted responses to the PANDORA regimen. In a retrospective post hoc analysis of the COU-AA-302 trial, 100 men who had received abiraterone on study were subsequently treated with docetaxel. The unconfirmed ≥50% PSA response rate was 40%, and the confirmed ≥50% PSA response rate was 27% [25]. These results have been corroborated in several other retrospective reviews of men treated with docetaxel following abiraterone, with a ≥50% PSA decline ranging from 13%–48% [26–30]. In murine xenografts of enzalutamide naive and resistant tumors, docetaxel inhibited tumor growth in the naive tumors but not in the resistant xenografts [31].

The majority of men enrolled on PANDORA had received multiple lines of treatment. These men had typical age and performance status for those treated with docetaxel in the castration-resistant setting. The proportion of men who reported an improvement in pain scores and quality of life is consistent with results from previous chemotherapy studies [24, 32]. Men with mCRPC treated in routine clinical practice with docetaxel at Princess Margaret Cancer Centre had an overall survival of 13.6 months [33]. The overall survival of patients enrolled on PANDORA was higher (15.8 months), although it was shorter than that reported in the TAX327 trial or patients treated on other trials at Princess Margaret Cancer Centre [24, 33]; these men had not received prior treatment with abiraterone or enzalutamide.

Serious adverse events were infrequent in men receiving the PANDORA regimen. The main hematologic toxicity was anemia, with four men experiencing a grade 3 or greater adverse event and three men experiencing febrile neutropenia. Fatigue was the most common nonhematologic toxicity but was only severe in 24% of participants. Peripheral neuropathy occurred in 29% of men and was mild to moderate in severity. No unexpected toxicities were observed. The type and frequency of adverse events seen in this study were comparable with those reported for docetaxel and prednisone [24]. The combination regimen of high dose pantoprazole (240 mg IV Q3 weekly) with standard dose docetaxel and prednisone is a tolerable and safe schedule.

Nuclear staining of p62 was associated significantly with RECIST response, and there was a nonsignificant association between p62 nuclear staining and PSA response. These observations support the premise that higher autophagy produces greater resistance to docetaxel and fewer responses. However, these results must be interpreted with caution given the small number of samples tested. No associations were seen between p62 and LC3B staining. This study did not analyze samples from metastases and thus it is not known if p62 and LC3B expression would have been different and potentially associated with clinical outcomes. To our knowledge, there is scant data comparing expression of p62 and LC3B in primary tumor samples and metastatic tumor samples in prostate cancer. The Ca IX results did not corroborate the nuclear p62 findings, and Ca IX is known to be an imperfect measure of hypoxia. The docetaxel concentration was highly variable, which was consistent with previous pharmacokinetic analyses of docetaxel that have demonstrated high interpatient variability [34].

The PANDORA trial had several limitations. This single arm, nonrandomized study predefined ambitious endpoints in order to detect a strong signal of activity of high dose pantoprazole with docetaxel and prednisone in mCRPC. It would have been preferable to conduct a randomized phase II study of the experimental regimen compared with standard docetaxel with prednisone, to account for the reduced activity of chemotherapy following abiraterone and or enzalutamide pretreatment. Such a study would have required substantially more resources than were available to the investigators.

Therapeutic interventions with specific inhibitors of autophagy should be pursued, but clinical trial design must account for prior treatments and the resultant impact on response rates to docetaxel. The reality is this population of men with mCRPC who have not received either abiraterone or docetaxel is set to decrease further as both these agents are now being used to treat men with metastatic hormone sensitive prostate cancer (mHSPC) who fulfill specific criteria [35–37]. To account for this it may be necessary to use autophagy inhibitors earlier in the disease course, for example in mHSPC with docetaxel, although this would have several design challenges such as endpoint selection and the large numbers of patients that would be required to demonstrate a benefit. This trial could test contemporaneous diagnostic and on-treatment tumor tissue samples for autophagy markers, which may provide a more accurate assessment of autophagy inhibition.

Two factors that were not addressed by this study are how to accurately measure autophagy inhibition and the degree of autophagy inhibition that is required to produce

a meaningful clinical response. Both these issues need to be tackled in any future studies evaluating modulators of autophagy. In spite of the biomarkers measured in this study, currently no reliable biomarker exists to evaluate autophagy inhibition. Several autophagy inhibitors are being tested in clinical trials in a variety of advanced solid tumors, including prostate cancer [38]. These trials test combination schedules with autophagy inhibitors and chemotherapy or targeted treatment. It is not known if these autophagy inhibitors are superior to pantoprazole. Another potential consideration would be to substitute cabazitaxel for docetaxel, given limited evidence for lack of cross-resistance to cabazitaxel following treatment with abiraterone and or enzalutamide [31].

Conclusion

Our trial demonstrated that high dose pantoprazole combined with standard dose docetaxel and prednisone was tolerable and safe. Although the regimen was clearly active in men with mCRPC, the primary endpoint of confirmed ≥50% PSA decline in 75% of treated men was not reached, thus we did not proceed to the second stage of this Simon two-stage study and have not pursued the development of this schedule.

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Disclosures

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For Further Reading:
Xiao X. Wei, Adam P. Siegel, Rahul Aggarwal et al. A Phase II Trial of Selinexor, an Oral Selective Inhibitor of Nuclear Export Compound, in Abiraterone- and/or Enzalutamide-Refractory Metastatic Castration-Resistant Prostate Cancer. ***The Oncologist*** 2018;23:656–e64.

Abstract

Lessons Learned

- In abiraterone- and/or enzalutamide-refractory metastatic castration-resistant prostate cancer (mCRPC) patients, selinexor led to prostate-specific antigen and/or radiographic responses in a subset of patients, indicating clinical activity in this indication.
- Despite twice-a-week dosing and maximal symptomatic management, selinexor was associated with significant anorexia, nausea, and fatigue in mCRPC patients refractory to second-generation anti-androgen therapies, limiting further clinical development in this patient population.
- This study highlights the challenge of primary endpoint selection for phase II studies in the post-abiraterone and/or post-enzalutamide mCRPC space.

Background. Selinexor is a first-in-class selective inhibitor of nuclear export compound that specifically inhibits the nuclear export protein Exportin-1 (XPO-1), leading to nuclear accumulation of tumor suppressor proteins.

Methods. This phase II study evaluated the efficacy and tolerability of selinexor in patients with metastatic castration-resistant prostate cancer (mCRPC) refractory to abiraterone and/or enzalutamide.

Results. Fourteen patients were enrolled. Selinexor was initially administered at 65 mg/m2 twice a week (days 1 and 3) and was subsequently reduced to 60 mg flat dose twice a week (days 1 and 3), 3 weeks on, 1 week off, to improve tolerability. The median treatment duration was 13 weeks. At a median follow-up of 4 months, two patients (14%) had ≥50% prostate-specific antigen (PSA) decline, and seven patients (50%) had any PSA decline. Of eight patients with measurable disease at baseline, two (25%) had a partial response and four (50%) had stable disease as their best radiographic response. Five patients (36%) experienced serious adverse events (SAEs; all unrelated to selinexor), and five patients (36%) experienced treatment-related grade 3–4 AEs. The most common drug-related adverse events (AEs) of any severity were anorexia, nausea, weight loss, fatigue, and thrombocytopenia. Three patients (21%) came off study for unacceptable tolerability.

Conclusion. Selinexor demonstrated clinical activity and poor tolerability in mCRPC patients refractory to second-line anti-androgenic agents.